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Formulation, Development and Evaluation of Oral Dispersible Tablet of Antispasmodic Drug Alverine

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ABSTRACT:

Optimizing medication administration to achieve maximum therapeutic effectiveness while minimizing adverse effects is pivotal for desired outcomes. This study delves into the development of a viable dosage form through a comprehensive exploration of physicochemical mechanisms governing a specific medication. Orally dissolving tablets (ODTs) have emerged as a promising option, especially for individuals facing difficulties swallowing conventional pills due to dysphagia, a condition prevalent among various age groups, notably the elderly and those with neurological disorders. ODTs offer advantages by dissolving in saliva without the need for water, enhancing accessibility for diverse patient populations. They have been studied extensively for their potential to modify drug-dissolving profiles, enhance bioavailability, and improve patient compliance, particularly by masking the unpleasant taste of active compounds.

Numerous techniques, including lyophilization, molding, freeze-drying, and direct compression, have been utilized to develop commercially available ODTs. Recent advancements such as the WOW tab technology, flash tab technique, and orosoly procedures showcase innovative approaches protected by patents.

In this investigation, Alverine orodispersible tablets were formulated using specific disintegrants and the direct compression method, yielding nine formulations meeting acceptable pre-compression parameters. Compatibility studies confirmed the integrity of Alverine without any drug-excipient interactions. Among the formulations, P4 and P7 exhibited superior characteristics such as high hardness, low friability, and rapid disintegration, aligning with the desired attributes of an orodispersible tablet. Dissolution tests indicated optimal drug release profiles, suggesting enhanced bioavailability from these formulations.

The study concludes that Alverine orodispersible tablets meet the criteria for an effective orodispersible dosage form, presenting a viable alternative to conventional tablets, ensuring potential therapeutic benefits and improved patient acceptability.

Keywords: Oral Dispersible Tablets (Odts), Medication Administration, Dysphagia, Bioavailability, Patient Compliance, Drug-Excipient Interactions, Formulation Techniques.

1. Introduction

The medication should be administered to take effect at a rate and a focus that maximises therapeutic effectiveness while reducing unfavourable impacts to get the desired outcome. To make a workable dosage form, conduct a thorough investigation of the physicochemical mechanisms that govern a certain medication There should be some formulation. The most common method of taking medications is through the typical and advised method of medicine administration for both liquid and solid dose forms. Orally dissolving pills [ODT] solid, single-unit dose forms that can be ingested to disperse/dissolve in saliva, followed by a dry swallow. Dysphasia, or trouble swallowing, affects people of all ages. groups, particularly the elderly, and can even be noted while consuming customary capsules and pills. This illness is related to a number of severe conditions, such as stroke and Parkinson's disease, AIDS as well as other neurological conditions including cerebral palsy. ODT is easy to give because it doesn't require water to take the pills, making it suitable for children, the elderly, and patients on the move. [1-3] ODTs have been studied for their potential to alter the drug's dissolving profile, increase the bioavailability of poorly water-soluble medicines, and boost patient compliance. As a result, disguising the\staste of unpleasant active compounds is a big barrier\sto overcome to create ODT products properly. In conclusion, oral administration of bitter active ingredients by ODT formulations ought to increase patient compliance, improve palatability, and have a positive therapeutic effect.[1,4,5]

Several techniques, including lyophilization, moulding, freeze drying, sublimation, rapid dissolving films, and direct compression, are used to create commercially available ODT. moulding and lyophilization. The WOW tab technology, flash tab technique, Zydus, and orosoly procedures are a few recent examples of unique preparation methods for orodispersible tablets that have been developed as patent technology for ODT. The current study highlights the production, properties, and advantages; the inclusion of medications in ODT; and assessments of the orally disintegrating tablet. [6]

2. Materials And Methods

Drug Alverine is purchased from Manus Aktteva Biopharma LLP Ahmedabad, Gujarat, India and all other materials like Mannitol, Magnesium steric acid, Microcrystalline Cellulose 101, Starch 1500, Maize starch, Polyplasdone XL 10, Meglumine, Lactose monohydrate from Central Drug House in New Delhi.

Pre-Formulation

Pre-formulation studies are the first step in drug dose sorting. The primary goal of pre-formulation studies was to generate data that would be useful in the manufacturing of formulations and dose structures.

Organoleptic Parameter of Drug

Table 1 lists the morphological parameters that have been determined based on physical observations.

Table 1. Organoleptic parameters of the drug

S.NO	Organoleptic parameter	Result
1	Shade	Colourless
2	Taste	Tasteless
3	Bouquet	Nothing
4	Personified	Crystalline power
5	Melting point	Literature reported- 100-1020C
		By capillary method- 99-1000C

Determination of Melting point

A capillary tube that had been filled with the medication Alverine through a sweeping end was sealed using a Bunsen burner. Subsequent to embedding the medication-filled fine cylinder into the dissolving point contraption, the temperature at which the medication began to not entirely settle. Alverine's melting point was discovered to be between 99 and 1000C.

Fourier transform infrared [FTIR] spectroscopy

The Alverine IR spectrum was obtained using FTIR [Jasco]. The chromatogram's reported characteristic peaks are listed in Table 3.10. Minor variations in drug peaks were observed. Figure No. 1 depicts the drug sample's infrared spectra.

Table 2 FTIR of Alverine

S. No.	Type of stretching vibration	Frequency[cm^{-1}]
		Experimental
1	Aromatic [C-H]	3200
2	C-H	3000
3	N-H	3300

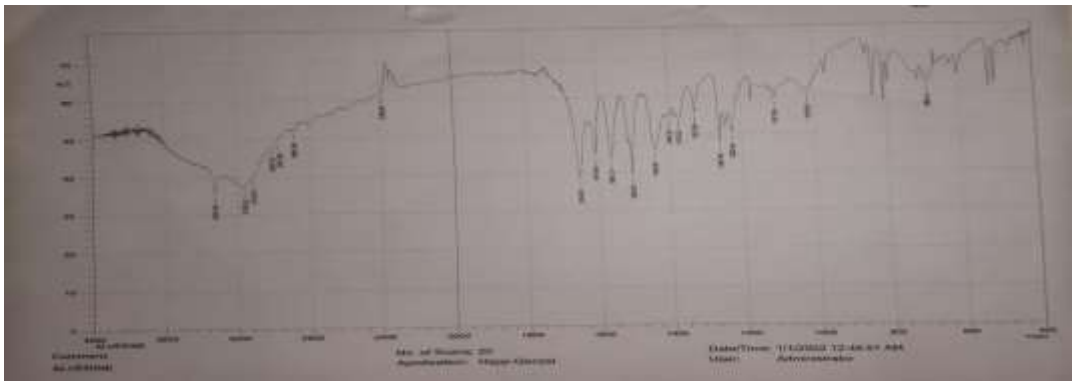


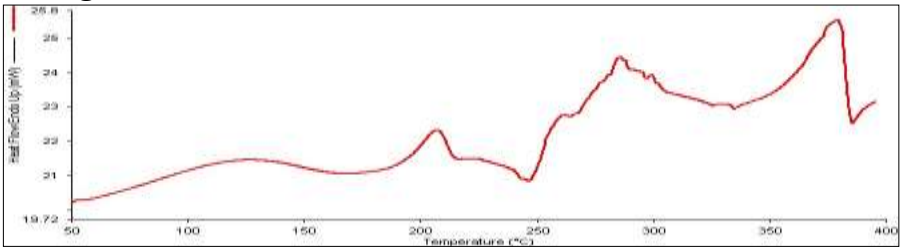
Fig No. 1 FTIR Spectra

DSC Study:

DSC was conducted to assess the thermal properties of this medication. Require [5-10mg] sample sealed to a hermetically aluminium pan. In that, the DSC spectra sharp endothermic

peak of fusion of Alverine detected at 100 to 210^{o}Cwhich is equivalent to its melting point.

DSC of pure drug Alverine



[i] DSC of Alverine

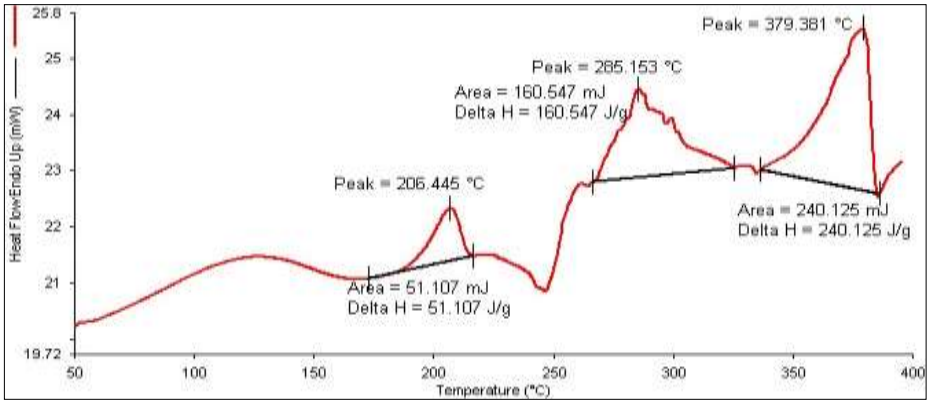


Fig No. 2 DSC of Alverine

[ii] DSC of Alverine

Ultraviolet (UV) absorption spectra in ethanol and phosphate buffer

The resulting value of λmax was compared to Volume 2 of Clarke's Analysis of Drug and Poison and the official monograph (BP). The maximum amount of Alverine found was 253 nm, which was similar to the maximum amount of Alverine published by the British Pharmacopeia, which is 253 nm.

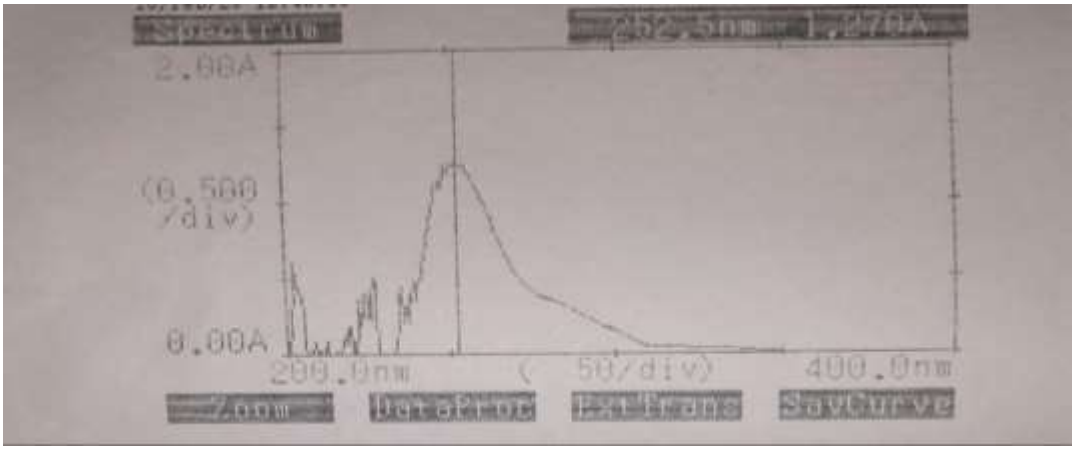


Fig. No. 3 Alverine in ethanol has a UV spectrum.

TABLE 3: Alverine calibration curve in ethanol

Serial no.	Conc. (µg/ml)	Absorbance
1	0.5	0.094
1	1	0.172
3	1.5	0.254
4	2	0.354
5	2.5	0.441
6	3	0.549

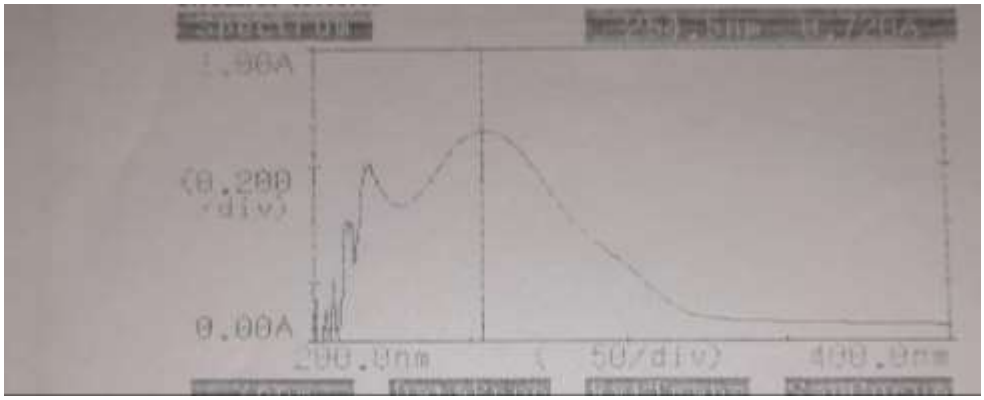


Fig 4: Alverine absorbance curve in phosphate buffer pH6.8

TABLE 4: Alverine calibration curve in phosphate buffer pH6.8

Concentration mg/ml	Absorbance
5	0.0159
10	0.035
15	0.052
20	0.069
25	0.083
30	0.098

Analytical method: The UV spectroscopy-based analytical methods yielded the following results:

Preparation of Standard and Stock Solution: The Alverine standard and stock solutions in ethanol were successfully formulated for use in future research.

Determination of λ max: The UV spectrum was used to calculate the Alverine λ max in each solvent [ethanol and Buffer 6.8]. In ethanol and Buffer 6.8, Alverine had maximum absorbance at 252.5nm and 254.5nm, respectively, which was consistent with the reported value. These Alverine maximum values were used for all UV spectrophotometric analyses.

Preparation of Calibration Curve: In ethanol and methanol, a calibration curve was plotted, yielding the following results:

Calibration curve in ethanol

The absorbance of various aliquots ranging from 10-100 µg/ml prepared from the drug standard solution (Alverine) was measured at 243nm against an ethanol reference blank using a UV spectrophotometer.

The calibration curve of Alverine absorbance vs concentration in ethanol was plotted. After the data was analyzed, statistical parameters such as the regression coefficient [R^2], equation of the line, and slope were calculated from the curve. The graph revealed a linear relationship over the given concentration spectrum.

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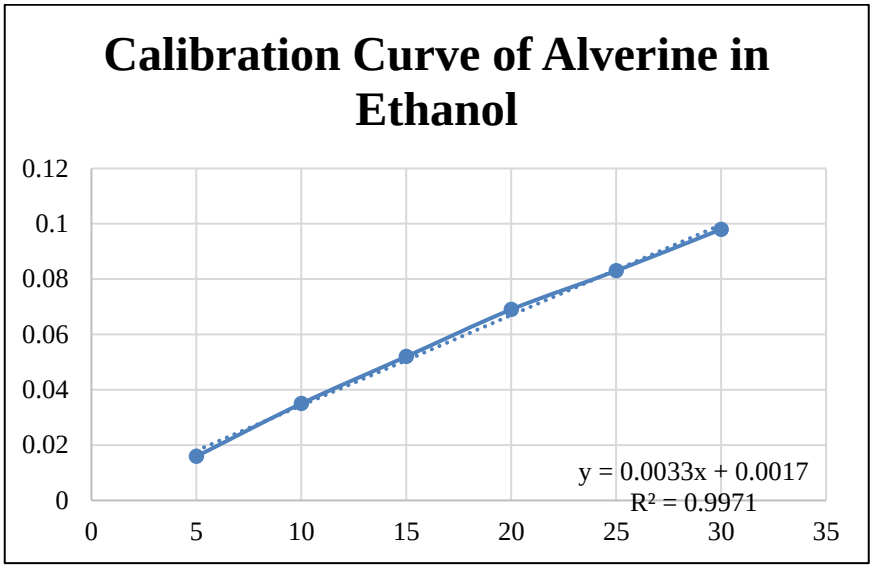

Figure 5 - Calibration Curve of Alverine in Ethanol

Table 5 Statistical parameter obtained from the calibration curve in ethanol

Statistical parameter	In ethanol
R^2	0.9971
Slope	0.0033x
Equation of line	y = 0.0033x + 0.0017

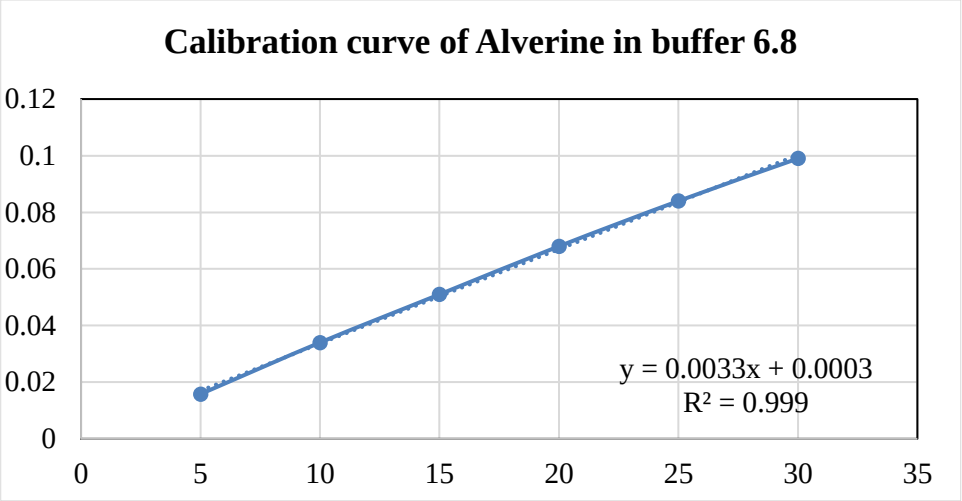

Fig 6 - Calibration curve of Alverine in buffer 6.8

Table 6 Statical parameters obtained from the calibration curve in methanol

Statistical parameter	In buffer 6.8
R^2	0.999
Slope	0.0033
Equation of line	Y= 0.0033x+0.0003

Surface characteristics

- **Particle size and particle distribution**

Decisions about a molecule's dimensions should be made both in the pre-formulation function and the formulation function because they are crucial for small molecular sizes.
A microscope is used to measure the Alverine particle size.

Table 7: Identify the average Alverine size of the particles.

S.NO.	Size of the particle	Typical size range [d]	Number of particles in each size category	N x d
1	0-5	2.59	72	186.48
2	5-10	6.85	14	95.9
3	10-15	12.96	7	90.72
4	15-20	16.18	2	32.36
5	20-25	23.7	1	23.7
6	25-30	21.83	1	21.83

Solubility

Solubility is generally decided in regularly utilized solvents and a few oils if the molecule is lipophilic.

Determination of the saturation solubility of the drug in ethanol, buffer and distilled water for excipient selection.

The drug's maturation solubility in various ethanol, buffer and distilled water will be set by the shake flask method.

Table 8: Solubility study

S.no.	Component	% Release	Solubility
1	Ethanol	487.42/10ml	Soluble
2	Phosphate buffer 6.8	461/10ml	Soluble
3	Distilled water	1268.58/10ml	Very slightly soluble

Tapped Density

The following formula can be used to compute Tap Density:

Tapped Density is equal to the weight of the powder/volume of the tapped packing

Table 9: Tapped density

S.no.	Batch No.	Tapped density
1	P1	0.294
2	P2	0.312
3	P3	0.25
4	P4	0.33
5	P5	0.28
6	P6	0.3
7	P7	0.32
8	P8	0.3
9	P9	0.31

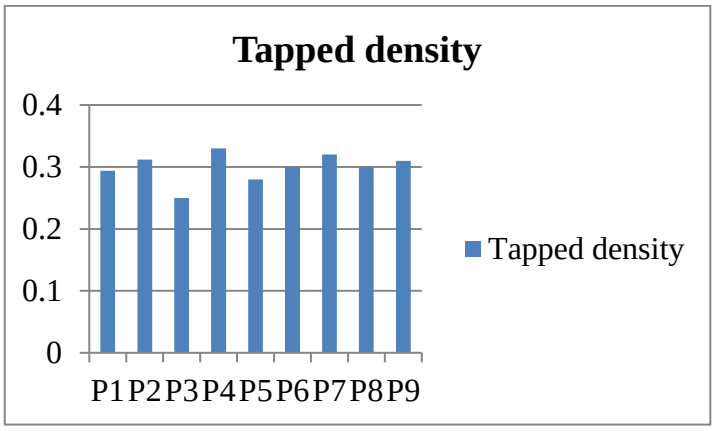

Fig. No. 7 – Graph of Tap Density

Bulk Density

The formula below can be used to compute bulk density:

Bulk density is equal to [Weight of the powder / Volume of the packing]

Table 10: Bulk density

S.no.	Batch No.	BD
1	P1	0.127
2	P2	0.138
3	P3	0.163
4	P4	0.2
5	P5	0.16
6	P6	0.166
7	P7	0.177
8	P8	0.172
9	P9	0.179

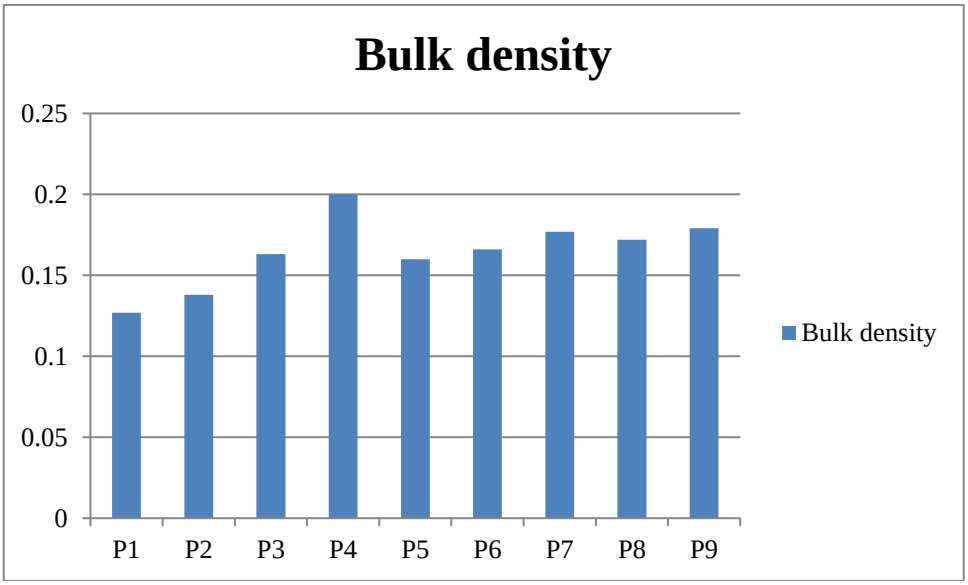

Fig. No. 8 – Graph of Bulk Density

Angle of repose

The angle of repose is the angle made by a material, with respect to the horizontal when piled. It is used to check flow property of powder. The angle of repose is determined using the equation below.

Tan Θ = h/r

Table 11: Angle of repose

S.no.	Batch No.	Angle of repose

1	P1	21.77
2	P2	22.54
3	P3	22.08
4	P4	20.42
5	P5	21.51
6	P6	22.24
7	P7	20.56
8	P8	21.21
9	P9	20.58

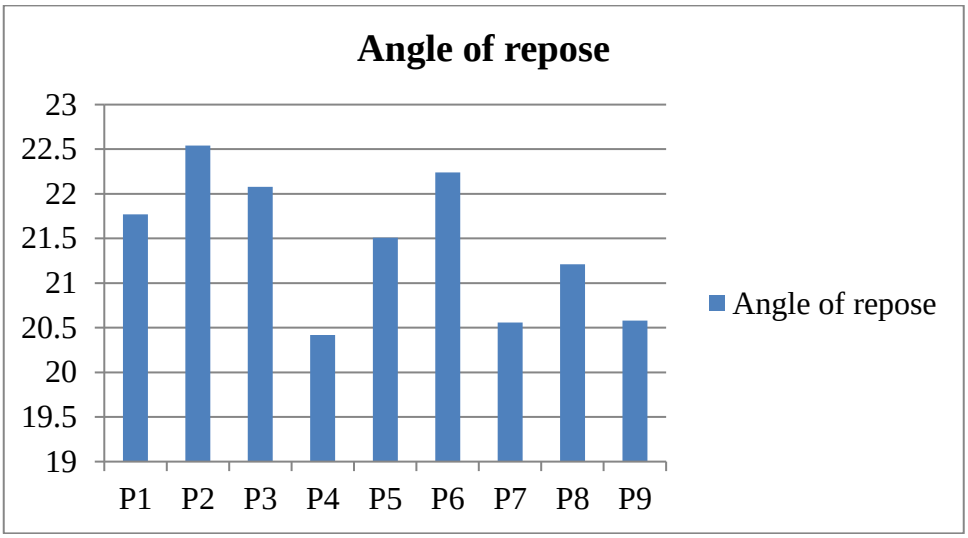

Fig. No. 9- Graph of Angle of Repose

2.1.11 Carrr's Index -

Formula used for it is :

Percentile Carrr's Index is equal to [[TD-BD] X 100] / TD]

Table 12: Carrr's Index [Compressibility index]

S.no.	Batch No.	Carr's index
1	P1	14.147
2	P2	24
3	P3	20.303
4	P4	11.217
5	P5	25.503
6	P6	13.355
7	P7	11.428
8	P8	13.333
9	P9	11.65

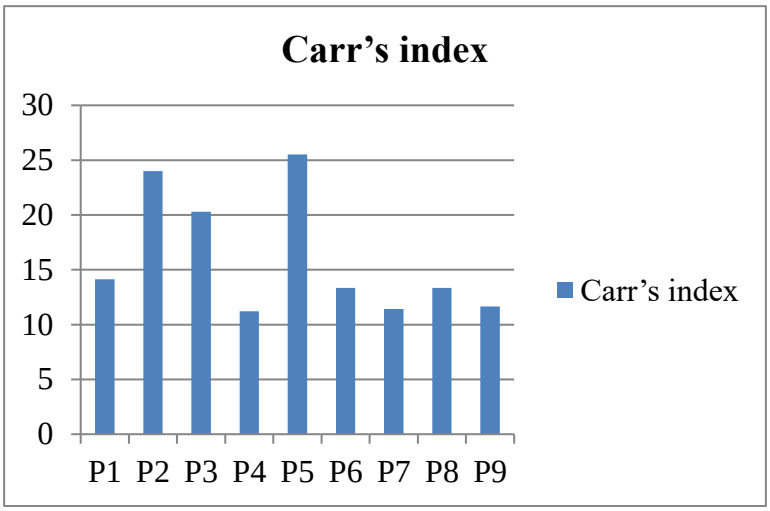

Fig No.10- Graph of Carr's Index

2.1.11 Hausner's ratio

One can determine Hausner's ratio by:
Hausner's ratio = [Tapped density x 100]/ [Poured density]

Table 13: Hausner's Ratio

S.no.	Batch No.	Hausner Index
1	P1	1.296
2	P2	1.326
3	P3	1.47
4	P4	1.253
5	P5	1.418
6	P6	1.359
7	P7	1.28
8	P8	1.458
9	P9	1.429

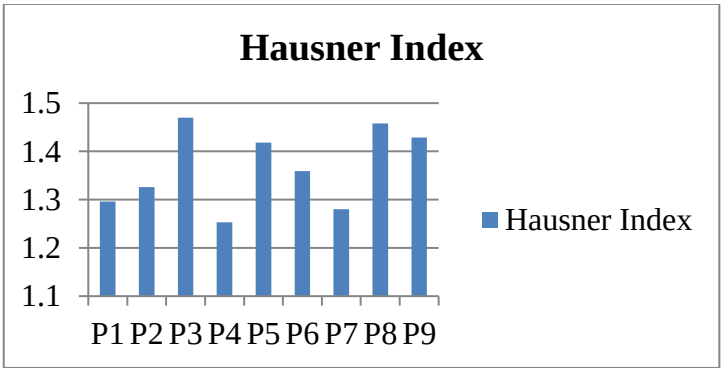

Fig No. 11 - Graph of Hausner's Ratio

Method of Preparation of OrodispersibleTablets

DIRECT COMPRESSION PROCESS is used to process oral dispersible tablets.
The steps below are used-

- Alverine was mathematically joined with lactose, microcrystalline cellulose, and strainer no.40.
- This blend was then consolidated in a fast blender granulator with starch and ferric oxide yellow.
- To make the folio arrangement, hydroxypropyl methylcellulose was disintegrated in separated water while being blended.
- The speedy blender granulator was utilized to add this cover answer for the combination.
- The granular mass was air dried for 5 to 10 minutes prior to being additionally dried at 45 to 55 degrees Celsius. for five to ten minutes, then went through sifter number 10.
- Dry grains were vibratory sifted by means of sifter number 30.
- The dried granules were joined with HPMC and magnesium stearate in dry blender.
- In a tablet punching machine, these greased up grains were compacted to make tablets.

Table 14: Formulation table of Alverine tablets

Additives	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**
Alverine	21	21	21	21	21	21	21	21	21
Mannitol	1	1	1	1	1	1	1	1	1
Magnesium steric acid	1	1	1	1	1	1	1	1	
Microcrystalline Cellulose 101	45	40	45	40	45	40	45	40	43
Starch 1500	------	------	10	15	-----	10	------	15	10
Maize starch	10	15			10		10		
Polyplasdone XL 10	20	20	20	20	20	20	20	20	20
Meglumine	1	1	1	1	1	1	1	1	1
Lactose monohydrate	1	1	1	1	1	1	1	1	1
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total	100	100	100	100	100	100	100	100	100

Table 15: Mass variations between batches of various formulations

S.No.	**Formulations**	**Total wt. [in gm]**	**A1**	**A2**	**A3**	**A4**	**A5**
1	P1	0.52	0.11	0.12	0.11	0.11	0.11
2	P2	0.53	0.11	0.12	0.11	0.11	0.11
3	P3	0.54	0.12	0.12	0.12	0.12	0.12
4	P4	0.53	0.12	0.12	0.11	0.11	0.11
5	P5	0.59	0.09	0.12	0.15	0.15	0.15
6	P6	0.51	0.12	0.12	0.11	0.11	0.11
7	P7	0.53	0.11	0.12	0.12	0.12	0.12
8	P8	0.52	0.10	0.12	0.10	0.10	0.10
9	P9	0.49	0.12	0.12	0.09	0.09	0.09

Friability

Percentage Friability of tablets is measured–

Percentage Friability = W1 – W2 /W1 × 100

Table 16: Friability

S.No.	Batch No.	Friability [%]
1	P1	0.24
2	P2	0.23
3	P3	0.21
4	P4	0.17
5	P5	0.18
6	P6	0.19
7	P7	0.18
8	P8	0.22
9	P9	0.20

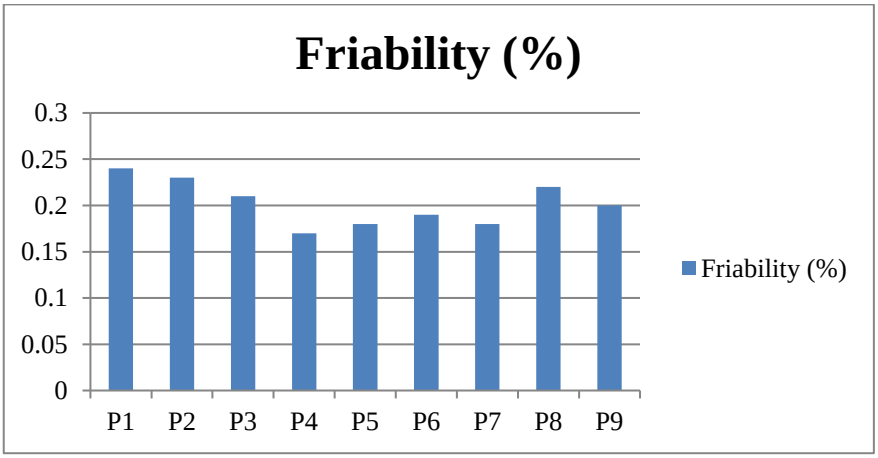

Fig No. 12 – Graph of % Friabillity

Hardness:

The hardness of tablets is assessed using hardness testers made by Pfizer.

Table 17: Hardness

S.No.	Batch No.	Hardness [kg/cm^{2}]
1	P1	2.14±0.268
2	P2	2.76±0.272
3	P3	2.115±0.37
4	P4	2±0.356
5	P5	3.065±0.215
6	P6	2.7±0.304
7	P7	2.1±0.308
8	P8	3.05±0.215
9	P9	2.18±0.402

In-vitro Disintegration time

The time it took for each pill to completely dissolve and leave no discernible bulk in the apparatus was measured in seconds. [Table 18]

Table 18: Disintegration time

S.No.	Batch No.	D.T [min]
1	P1	1.2
2	P2	1.50
3	P3	0.55
4	P4	0.39
5	P5	0.50
6	P6	1.04
7	P7	0.42
8	P8	1.02
9	P9	1.09

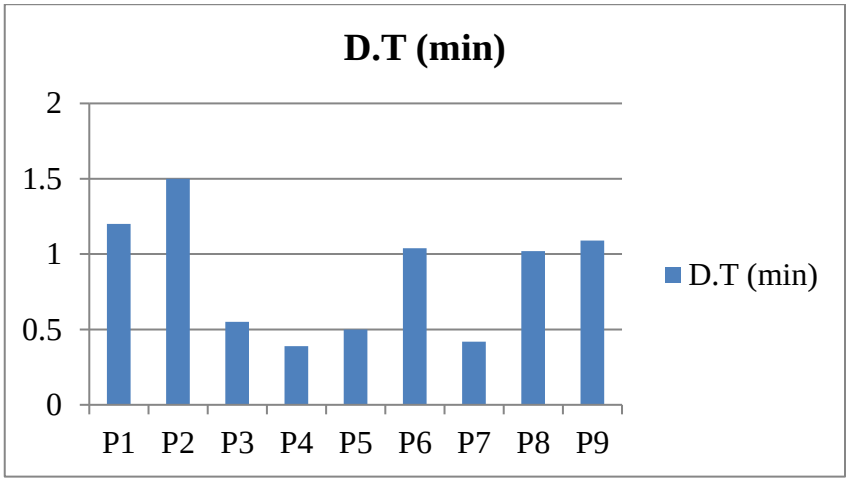

Fig No. 13 – Graph of D.T [min.]

In-Vitro Dissolution Studies

Tablet mixes were completed, and micrometric readings were performed on those mixtures. The calibration curve has a regression value of 0.9997. The formulation's test upsides were seen in the range of 97.8 to 102.3%. Following similarity analyses, it was determined that all of the used fixes were compatible with the d. Magnesium steric acid, polyplasdone XL 10, and 20% binder were combined to create formulation [P8]. The results revealed that the disintegration was within tolerances and that a 30-minute window was required for a complete medication release. Plan [P8] was therefore regarded as an improved definition. Speed-up security reads were performed for this bunch. Measure and disintegration read were performed for the advanced plan [P-8] at various time spans. All of the borders were considered to be acceptable, however disintegration experiments revealed that describing P8 has produced the finest results.

Table 19: Dissolution profile of different formulations [P1-P9]

Time (min)	P1	P2	P3	P4	P5	P6	P7	P8	P9
5	22.49±0.13	18.61±0.67	29.9±0.28	27.4±0.73	21.85±0.55	18.98±0.56	33.03±0.56	33.03±0.28	27.67±0.63
10	35.70±0.59	33.18±0.89	49.1±0.25	43.8±0.25	39.54±0.26	34.89±0.05	54.61±0.23	65.68±0.39	45.178±0.023
15	41.2±0.49	38.62±0.59	57.9±0.035	51.6±0.37	42.032±0.77	41.54±0.36	59.6±0.46	76.64±0.33	58.96±0.37
20	47.1±0.48	43.64±0.53	64.7±0.73	58.6±0.29	50.99±0.59	46.58±0.78	68.09±0.42	82.39±0.85	69.83±0.16
30	52.7±0.52	49.94±0.72	78.23±0.14	69.17±0.89	53.98±0.47	48.94±0.48	79.90±0.29	91.86±0.42	81.64±0.34
45	57.6±0.55	54.7±0.22	82.7±0.83	74.7±0.39	58.89±0.32	56.47±0.25	84.42±0.53	99.03±0.78	84.87±0.21
60	79.9±0.32	72.4±0.64	91.7±0.23	84.14±0.83	82.07±0.38	79.64±0.71	93.13±0.89	100.46±0,54	92.12±0.16

Table 20 : Comparitive studies of formulation P4 and P7

Time (Min)	P4	P7
0	0	0
5	27.4	33.03
10	43.8	54.61
15	51.6	59.6
20	58.6	68.07
30	69.17	79.9
45	74.7	84.42
60	84.14	93.13

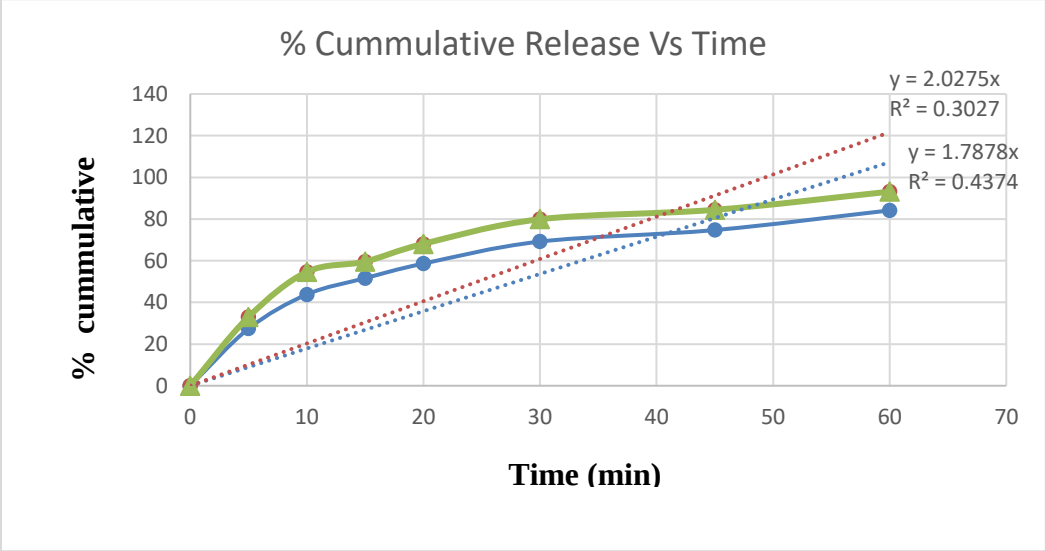

Fig No. 14 % Cumulative Release

Tablet thickness

Evaluate tablet thickness, and put it between two arms of the Varnier Caliper. (table 21)

Table 21: Thickness

S.No.	Batch No.	Thickness (mm)	Wetting Period (minutes)	Assay (%)
1	P1	2.75±0.01	2.12	97.8
2	P2	2.27±0.05	3.9	99.4
3	P3	2.176±0.08	1.53	98
4	P4	2.06±0.02	0.43	101.8
5	P5	2.71±0.07	1.81	99.7
6	P6	2.29±0.013	1.21	98.9
7	P7	2.156±0.016	0.38	102.3
8	P8	2.235±0.012	1.52	99.9
9	P9	2.245±0.015	1.41	99.1

Wetting time

A shorter wetting period suggests that the pill will degrade more quickly. The retention time was determined using the method that was provided. [table 3.33].

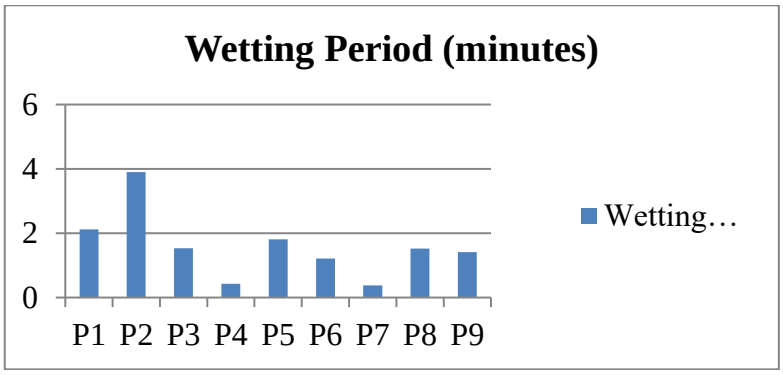

Fig No. 15– Graph of Wetting Time

Content uniformity

The formulation batches P4 and P7 were discovered to easily meet the requirements for the test.

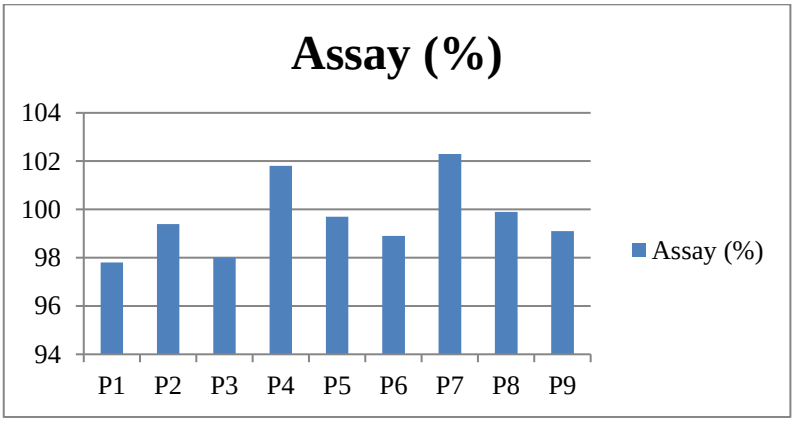

Fig No. 16 – Graph of Assay [%]

Stability Studies

According to the stability report, the potential is identified in the physical, chemical, effective, and toxicological determinations. According to ICH guidelines, the current study's soundness investigation was carried out in a dependability chamber using improved Alverine at stop temperature [4°C±1°C], room temperature [25°C±1°C and 60%±5% RH], and a temperature of [45°C±2°C and 75%±5% RH]

Table 22: Accelerated stability studies of optimized formulation At 45 ± 2^0 C & 75±5%RH

S.No.	Time period	% Drug release			
		Time (min)			
		10	15	20	30
1	Initial	63±0.23	83±0.72	92±0.28	99±0.32
2	1st month	65.7±0.58	82.2±0.69	92±0.53	98.7±0.17
3	2nd month	65.6±0.26	82.3±0.66	91.5±0.68	98.6±0.44
4	3rd month	65.3±0.36	81.8±0.32	91.4±0.47	98.3±0.54

3. Conclusion

Alverine orodispersible tablets were made in this investigation employing Magnesium steric acid, Microcrystalline Cellulose 101, and Polyplasdone XL 10 as disintegrants. The direct compression approach was used to create a total of nine formulations. The tested pre-compression parameters were within the permitted limits, indicating satisfactory free-flowing characteristics. IR spectroscopy was utilised to investigate drug-excipient compatibility and validated Alverine's undamaged structure, indicating no drug-excipient interaction.

Among the formulation tablets of batch P4 and P7, this formulation was considered to be the best in comparison to other formulations because it demonstrated high hardness, low friability, and the shortest wetting and disintegration time, which is an ideal attribute of a dispersible type tablet. The cumulative percentage of drug released for formulation batches P4 and P7 determined by the dissolving test demonstrates that the formulations had superior drug release towards the end, indicating good bioavailability of the medication from these formulations.

It was determined that Alverine orodispersible tablets could be effectively made since they met all of the criteria for an orodispersible tablet and would be a viable alternative to the already available conventional tablets.

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